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CASE REPORT

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Immune checkpoint inhibitor-induced autoimmune limbic encephalitis with positivity for anti-Hu antibodies in a patient with small-cell lung cancer: A case report and literature review

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Abstract

In recent years, there has been an increasing number of studies on neurological symptoms induced as paraneoplastic neurological syndrome (PNS) or neurological immune-related adverse events (irAEs) in patients treated with immune checkpoint inhibitors (ICIs). Herein, we report a 68-year-old male patient with small-cell lung cancer who developed memory impairment and autonomic nervous system dysfunction after three courses of carboplatin, etoposide, and durvalumab therapy. Brain magnetic resonance imaging revealed hyperintense areas restricted to the bilateral temporal lobes. Moreover, based on the blood test results, the patient was strongly positive for anti-neuronal nuclear antibodies. Hence, he was diagnosed with autoimmune limbic encephalitis (ALE). Corticosteroid pulse therapy was administered. After treatment, the patient exhibited gradual improvement in memory impairment. However, while tapering the prednisolone dose, the patient exhibited relapse of memory disturbance owing to ALE. It is challenging to distinguish PNS from neurological irAEs. However, ICI-induced ALE with positivity for anti-Hu antibodies has an extremely poor prognosis.

INTRODUCTION

The combined use of immune checkpoint inhibitors (ICIs) and chemotherapy is an effective treatment option for patients with extensive-disease small-cell lung cancer (ED-SCLC). However, the number of paraneoplastic neurological syndrome (PNS) cases has been increasing in patients with SCLC treated with ICIs. In patients with SCLC who develop neurological symptoms after ICI treatment, PNS is difficult to distinguish from neurological immune-related adverse events (irAEs). ICIs can stimulate the immune response to neuroantigens associated with PNS, leading to the development of undetected PNS.[1,2]

Herein, we report a case of ED-SCLC in a patient with ICI-induced autoimmune limbic encephalitis (ALE) with anti-Hu antibody positivity complicated by memory impairment and autonomic neuropathy.

CASE REPORT

A 68-year-old male patient with a 48-year history of smoking visited his previous physician due to a chief complaint of cough and dyspnea for 1 month. The patient had a history of chronic obstructive pulmonary disease and no history of autoimmune diseases. Chest computed tomography (CT) revealed a left hilar mass and swelling of the mediastinal and bilateral supraclavicular lymph nodes (Figure 1A). Hence, the patient was referred to our institution. Ultrasound-guided biopsy was performed for enlarged lymph nodes on the left

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side of the neck. Based on the examination results, the patient was diagnosed with SCLC. ^{18}F-fluorodeoxyglucose positron emission tomography revealed multiple liver and bone metastatic tumours. However, brain magnetic resonance imaging (MRI) did not reveal abnormal findings (Figure 2A). Therefore, the patient was diagnosed with ED-SCLC and treated with carboplatin, etoposide, and durvalumab. CT scan performed after two treatment cycles revealed that the primary and metastatic tumours had partial remission (Figure 1B).

On the 13th day after the third cycle, the patient was referred to our institution due to memory impairment that was severe enough to prevent him from driving a car. Neurological examinations and blood tests did not reveal significant findings. However, chest CT scan revealed that the size of the primary lesion continually decreased (Figure 1C). Brain fluid-attenuated inversion recovery (FLAIR) MRI (Figure 2B) revealed hyperintense areas restricted to the bilateral temporal lobes indicating limbic encephalitis. The PNS-related antibody tests showed high anti-Hu antibody levels. The cerebrospinal fluid tests showed cerebrospinal fluid pleocytosis and elevated protein and lactate dehydrogenase levels (Table 1). Based on the serological test, the patient tested negative for varicella-zoster virus, herpes simplex virus, and cytomegalovirus. Therefore, he was diagnosed with ALE.

The patient received corticosteroid pulse therapy and 1 mg/kg prednisolone as post-treatment. Thereafter, he presented with gradual improvement in memory impairment. In addition, he was encouraged to get out of bed. However, he experienced a transient decrease in blood pressure and loss of consciousness. Orthostatic hypotension were caused by an autonomic nervous system disorder. Thus, midodrine was administered, and the patient did not present with orthostatic hypotension.

However, while tapering the prednisolone dose, the patient experienced recurrence of memory impairment and orthostatic hypotension. Corticosteroid pulse therapy was administered again. However, the patient's memory

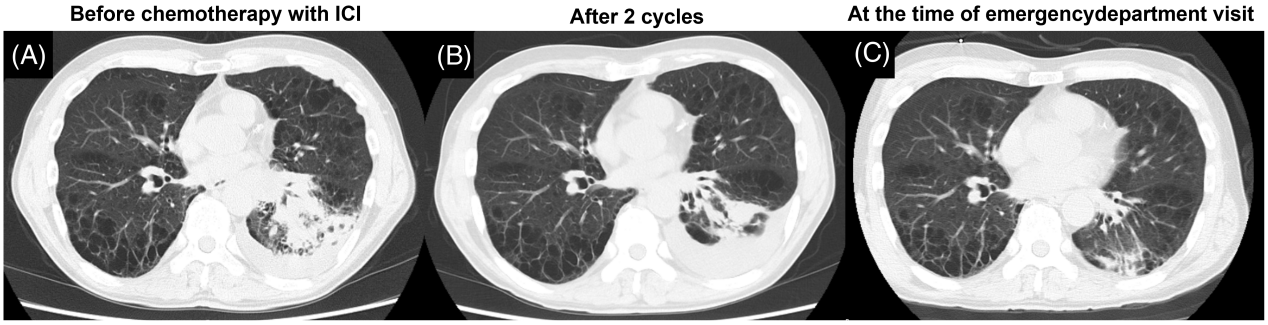

FIGURE 1 Comparison of computed tomography scan images before chemotherapy with immune checkpoint inhibitors (A) after two treatment cycles (B), and during emergency department visits (C). The size of the primary lesion and volume of the pleural effusion were decreased. No new shadows were observed.

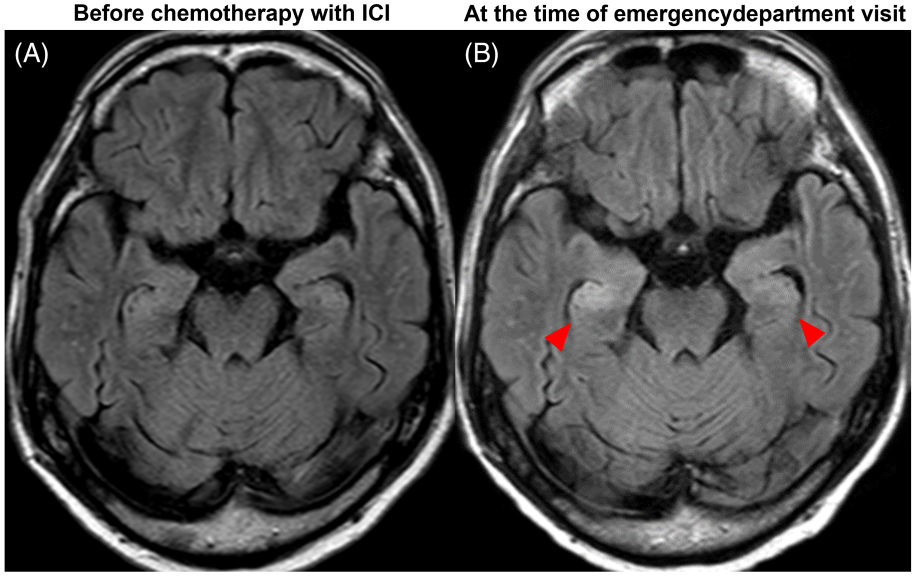

FIGURE 2 (A) Brain fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) before chemotherapy with an immune checkpoint inhibitor showing no abnormalities. (B) FLAIR imaging of brain MRI after the development of neurological symptoms showing high-intensity areas localized in the bilateral medial temporal lobes (red arrowheads).

impairment did not improve, and the high steroid dose could not be tapered. Consequently, the patient died from methicillin-resistant *Staphylococcus aureus*-related bacteremia.

DISCUSSION

In this case, the patient presented with memory impairment and orthostatic hypotension during combined therapy with chemotherapy and ICI for ED-SCLC. Moreover, he tested positive for anti-Hu antibodies. According to Graus, the diagnostic criteria for ALE are short-term memory impairment, seizures, and psychiatric symptoms that progress subacutely within 3 months of onset. Brain FLAIR MRI revealed high-signal areas limited to the bilateral temporal lobes and cerebrospinal fluid pleocytosis.[3] In this study, the patient met these criteria; hence, he was diagnosed with ALE.

PNS is difficult to distinguish from irAEs in patients with SCLC who develop ALE after ICI treatment. Symptoms of limbic encephalitis due to PNS are usually associated with SCLC progression; however, in this case, the shrinkage effect was sustained during the onset of ALE. Hence, the cause of ALE was believed to be neurological irAEs rather than PNS. In recent years, studies have reported the similarities between onset mechanisms of anti-Hu antibody-positive neurological irAEs and anti-Hu antibody-positive PNS. Patients with anti-Hu antibody-positive irAEs have a significantly higher mortality rate than those with anti-Hu antibody-positive PNS who were not treated with ICIs.[4] Moreover, the mortality rate of encephalitis as an irAE is 19%.[5]

TABLE 1 Laboratory findings at the onset of neurological symptoms.

Anti-neuronal antibodies		Cerebrospinal fluid		Serology	
Amphiphysin	Negative	Appearance	Clear	HSV-PCR	Negative
CV2	Negative	Cell count	25 μL	VZV IgG	Negative
PNMA2	Negative	Poly	62%	VZV IgM	Negative
Ri	Negative	Mono	38%	HSV IgG	Negative
Yo	Negative	Protein	140 mg/dL	HSV IgM	Negative
Hu	3+	Glucose	72 mg/dL	CMV IgG	Negative
Recoverin	Negative	Lactate dehydrogenase	43 IU/L	CMV IgM	Negative
SOX1	Negative	Creatine kinase	1 IU/L	JEV HI	Negative
Titin	1+			JEV CF	Negative
Zic4	Negative				
GAD65	Negative	Culture	Negative		
Tr	Negative	Cytology	Class I		

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; JEV, japan encephalitis virus; VZV, varicella-zoster virus.

TABLE 2 Autoimmune limbic encephalitis with anti-neuronal antibodies after immune checkpoint inhibitor treatment combined with chemotherapy.

No	Patient	Histology	ICI (number of doses)	Antibody	Symptoms	MRI findings	ALE treatment	ALE evolution	Ref
1	70F	SCLC	Atezolizumab (4)	Hu	Confusion Disorientation Memory impairment	FLAIR: hyperintense areas in the bilateral hippocampal	Methylprednisolone IVIG Rituximab	Partially Improved Relapse after 2 months	8
2	61 M	SCLC	Durvalumab (2)	$GABA_BR$	Cognitive impairment Convulsion	FLAIR: hyperintense areas in the left hippocampus	Methylprednisolone IVIG	Not improved	9
3	66 M	SCLC	Atezolizumab (3)	Hu Zic4	Disorientation Dysphagia Gait disturbance	FLAIR: hyperintense areas in bilateral temporal lobes	Methylprednisolone IVIG	Improved	10
4	72 M	SCLC	Durvalumab (8)	$GABA_BR_1$ GAD65	Disorientation Dysphasic	FLAIR: hyperintense areas in the left temporal lobe and hippocampus	Methylprednisolone Plasma exchange	Improved	11
5	68 M	SCLC	Durvalumab (3)	Hu Titin	Memory impairment Dysautonomia	FLAIR: hyperintense areas in the bilateral temporal lobes	Methylprednisolone	Partially Improved Relapse after 2 week	Present case

Abbreviations: ALE, autoimmune limbic encephalitis; ICI, immune checkpoint inhibitor; IVIG, intravenous immunoglobulins; MRI, magnetic resonance imaging; SCLC, small cell lung cancer.

In this case, steroid pulse therapy was administered in accordance with the treatment guidelines for autoimmune encephalitis.[6] However, it was not significantly effective. In general, if patients test positive for antibodies such as anti-Hu antibodies, which can identify intracellular antigens, response to immunotherapy is poor. Regarding the treatment of autoimmune encephalitis that develops after the use of ICIs, high-dose intravenous immunoglobulin (IVIG) therapy should be added to steroid therapy if the symptoms are severe and progressive. Furthermore, rituximab or blood purification therapy should be considered if there is no significant improvement in symptoms.[7] However, evidence supporting the efficacy of these treatments is insufficient.

Various neurological symptoms were observed in previous reports of SCLC with encephalitis after ICI treatment and chemotherapy (Table 2).[8–11] Patients were treated with steroids and IVIG in previous cases; a few cases improved, but some cases, such as our case, relapsed during steroid tapering. As the number of patients treated with ICIs increases, cases of relapse may also increase. The prognosis for patients who develop encephalitis in association with ICIs is poor. Thus, early diagnosis and treatment are crucial. Encephalitis as an irAE should always be considered, especially if a patient with SCLC presents with neurological symptoms after treatment with ICIs.

In conclusion, herein, we report a case of ALE during ICI administration in a patient with ED-SCLC. In patients who tested positive for anti-Hu antibodies, ICI treatment may cause neurological symptoms, which can lead to treatment resistance and poor prognosis. Therefore, it is important to consider the need to screen for paraneoplastic antibodies before ICI therapy is administered to patients with SCLC. To validate the association between irAEs-induced ALE and PNS-induced ALE and anti-Hu antibodies, a large-scale prospective study comparing the presence of anti-Hu antibodies and neurological symptoms before and after ICI therapy should be conducted.

AUTHOR CONTRIBUTIONS

Lynn Nakahara and Shun Matsuura wrote the manuscript, which was then reviewed by all co-authors.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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